

MS Handbook

Shauna F., diagnosed with
a relapsing form of MS




shared solutions®
1-800-887-8100

Understanding multiple sclerosis

Whether you are newly diagnosed and about to start a *relapsing multiple sclerosis (MS)* therapy, or are considering a change in your current therapy, this handbook is for you. It provides information to help you, along with your doctor and support team, determine which treatment will best fit your needs. We hope it answers some questions you may have along the way, including

- What is *MS*?
- What is the role of the *immune system* in *relapsing MS*?
- What are the different therapies available?
- What resources are available to me that offer support, guidance, and financial assistance?

As you read through this handbook, you will find words in *italics*. Definitions for these words appear in the glossary at the end of the handbook.

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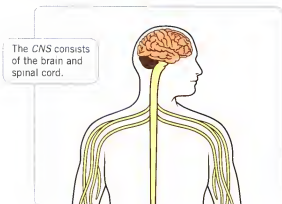
Please see Important Safety Information on pages 26 and 27, and full Prescribing Information on pages 28-39.

Maria Z., diagnosed with
a relapsing form of MS



MS overview

MS is a lifelong disease that involves the *central nervous system (CNS)* and the *immune system*.¹ Normally, the *immune system* defends your body from foreign invaders such as viruses and bacteria.² But in people with *MS*, the *immune system* attacks the nerve tissue in the *CNS*.¹



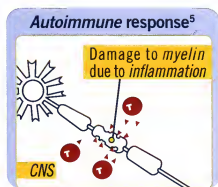
Let's look at the relationship between the *immune system* and *MS* more closely.

The *immune system* is a complex system made up of a vast network of cells and proteins that work together to provide your body with a natural system of defenses.²

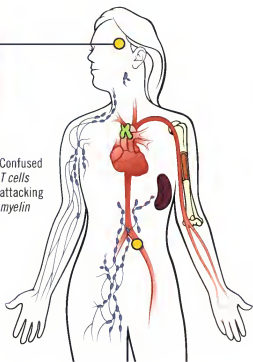
- The main cells involved in protecting your body are white blood cells, which travel throughout your body in the bloodstream to the lymph nodes, spleen, and thymus, looking for invaders³
- *T cells* are a type of white blood cell. They play an important role in protecting your body from invaders³

Relapsing MS is thought to be an autoimmune disease

In *relapsing MS*, *T cells* that normally protect the body from invaders (such as viruses and bacteria) become confused and attack the *myelin* that protects the nerve tissue in the *CNS*.⁴ This causes damage to the *neurons*.¹

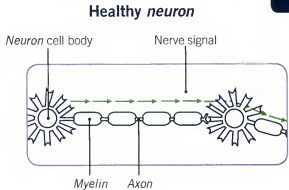


Confused
T cells
attacking
myelin

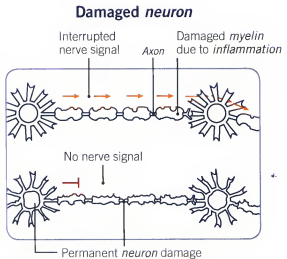


The impact of damage on the CNS

- *Neurons* send signals through the *CNS* to other parts of the body along nerve fibers called *axons*⁶
- These signals control physical functions like balance and muscle coordination, as well as memory and other *cognitive abilities*⁷



- When inflammatory *T cells* attack the *myelin*, they leave scar tissue called *scleroses (lesions)*¹
- This disrupts the body's ability to send signals from one part of the *CNS* to another, and causes *MS symptoms*¹




Symptoms you may experience with MS

The symptoms of *MS* are unpredictable and differ from one person to another. The symptoms you may experience vary based on the location and the extent of the damage to your *CNS*. It is not likely that you will experience all of the symptoms listed.⁷

You may find that you experience some of the symptoms at different times during the course of *MS*.⁷ The available disease-modifying *relapsing MS* therapies are not intended to treat the symptoms that accompany *MS*.⁸ Many of these symptoms can be managed with specific drug therapies, rehabilitation, and lifestyle strategies.⁷

The most common symptoms of *MS* are^{7,9}

- Weakness
 - Fatigue, lack of energy
 - Numbness
 - Tingling sensations
 - Walking, balance, and coordination problems
 - Dizziness
 - Blurred vision
 - Slurred speech
 - Bladder problems
 - Bowel problems
 - Depression
 - Memory loss, difficulty concentrating, and/or difficulty solving problems
- 

Possible causes of MS

Worldwide, *MS* may affect more than 2.3 million individuals¹⁰

Scientists have identified factors, based on the worldwide distribution of *MS*, that may provide clues to the possible causes of *MS*. These include the following:

Gender: Women are 2 to 3 times more likely to have *MS* than men.¹⁰

Genetics: *MS* is not directly inherited; however, the risk of getting *MS* rises in those who have a close relative (parent, sibling, or child) with *MS*.¹⁰

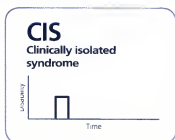
Age: Most people are diagnosed with *MS* between the ages of 20 and 50 years.¹⁰

Ethnic background: *MS* affects all races, but it is more common among people of northern European ancestry.¹⁰

Geography: *MS* is more common in areas farther north from the equator; it occurs less commonly in areas closer to the equator.¹⁰

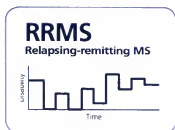
Disease courses in MS

*Clinically isolated syndrome (CIS)**



- A person with *CIS* may have experienced 1 attack, or event, of *MS*-like symptoms and have brain lesions consistent with *MS*¹¹
 - *CIS* is often an early indicator of *relapsing-remitting MS*¹¹
- Some *relapsing MS* therapies are approved for use to delay a second attack¹¹

*Relapsing-remitting MS (RRMS)**



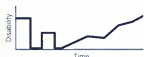
- Most common course of *MS*; affects approximately 85% of newly diagnosed people¹²
- Attacks, called *relapses*, are usually followed by partial or complete recovery¹²
- Symptoms may then be inactive for months or even years¹²

*Considered by the FDA to be relapsing forms of *MS*.

Secondary-progressive MS (SPMS)

SPMS

Secondary-progressive MS

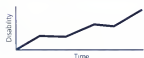


- Course of MS after RRMS¹²
- Occasional *relapses*; however, some symptoms remain constant with no remission¹²
- Progressive disability late in the course of SPMS¹²

Primary-progressive MS (PPMS)

PPMS

Primary-progressive MS

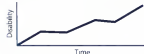


- Less common course of MS; affects approximately 10% of all people with MS¹²
- Slow onset, but nearly continuous worsening of condition¹²
- May level off at some point or continue for months or years¹²


Progressive-relapsing MS (PRMS)

PRMS

Progressive-relapsing MS



- Rarest course of MS; affects approximately 5% of all people with MS¹²
- Steady worsening of condition after diagnosis¹²
- Severe *relapses* with or without complete recovery¹²



Shauna F., diagnosed with
a relapsing form of MS

How your doctor determines if you have MS

MS is a complicated disease to diagnose. Many *MS* symptoms are similar to those caused by other conditions and may come and go, especially early on in the course of *MS*.^{7,13}

Your doctor, usually a *neurologist*, will take a number of factors into consideration when diagnosing *MS*. The starting points are a complete medical history, a neurological exam, and test results.¹⁴

One of the tests your doctor may order is an *MRI*, or *magnetic resonance imaging*, which takes highly detailed images of your brain and spinal cord to determine if you have the *lesions* typical of *MS*.¹⁴

No single test can provide a positive diagnosis of MS


When diagnosing *MS*, health care providers will look at a combination of factors and tests, which may include^{11,14}

- Changes in your strength and reflexes
- Your responses to touch, sound, and other stimuli
- The number of flare-ups, or attacks, you have over a period of time
- The number and types of *lesions* that can be seen on an *MRI*
- *Cerebrospinal fluid* analysis
- An *evoked potentials* test

The importance of early treatment

- Damage to the brain and spinal cord tissues can occur early in the *MS* disease course¹⁵
 - Even early on, permanent damage can occur
- The National Multiple Sclerosis Society (NMSS) recommends¹⁶
 - Considering therapy as soon as possible after a diagnosis of *relapsing MS*, or after a first attack for people at high risk of developing *MS*⁶

The importance of continued treatment

- Research confirms the importance of reducing *relapses* throughout the course of *relapsing MS*¹⁵
 - Even when you feel fine and are not experiencing symptoms, untreated *relapsing MS* may be causing irreversible damage in your *CNS*¹⁷
 - The NMSS recommends¹⁶
 - Continuing your therapy unless the side effects are too severe, the therapy is clearly not working, or there are medically appropriate reasons for changing to another therapy
- 

All relapsing MS therapies have the same goal

- Reducing the frequency of *relapses* to help minimize new damage to your *CNS*¹⁵





Bill S., diagnosed with
a relapsing form of MS

Understanding your options

An overview of approved *relapsing MS* therapies

All of the therapies approved to treat *relapsing MS*—as well as treatments currently being studied—are thought to have an impact on the *immune system*; however, they are thought to do so in different ways.^{5,18}

Make the choice, stay committed

Remember, the best choice for you depends on careful consideration of your individual needs and the recommendation of your doctor. Once you've found the right therapy for you, be sure to follow through. Staying committed to your treatment may be the best way for you to live your life to the fullest.

The therapies currently used to treat relapsing MS are^{19,20}

Aubagio® (teriflunomide)

Avonex® (interferon beta-1a)

Betaseron® (interferon beta-1b)

COPAXONE® (glatiramer acetate injection)

3-times-a-week COPAXONE® 40 mg

Daily COPAXONE® 20 mg

Extavia® (interferon beta-1b)

Gilenya® (fingolimod)

Novantrone® (mitoxantrone for injection concentrate)

Rebif® (interferon beta-1a)

Tecfidera® (dimethyl fumarate)

Tysabri® (natalizumab)

COPAXONE® is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Please see Important Safety Information on pages 26 and 27, and full Prescribing Information on pages 28-39.



Treatment considerations

You may already be taking a *relapsing MS* therapy, or you may be newly diagnosed and considering which *relapsing MS* therapy to choose. With so many variables to consider, determining a treatment strategy can be challenging, but making an informed decision begins by working with your doctor and knowing the questions to ask about each therapy. Examples of important questions to ask include

- ☐ **Effectiveness**
 - Is this therapy effective in reducing *relapses*?
 - Does this therapy have any impact on *MRI* measures?
 - How long has this therapy been available?
 - What are the risks and benefits associated with this therapy?
- ☐ **Tolerability**
 - What kind of side effects can I expect from this therapy?
 - How will this therapy fit into my days, weekends, and lifestyle?
- ☐ **Safety**
 - What can you tell me about the safety profile of this therapy?
 - How does this therapy work with my *immune system*?
- ☐ **Support**
 - What types of network and support are offered to those who take this treatment?

Glossary of terms

In this section, you will find the definitions of the words that appear in *italics* throughout this handbook. You may even refer to this glossary before an appointment with your *neurologist* in order to brush up on terms about *MS* and its treatment.

Autoimmune

A condition in which the body's *immune system* mistakenly attacks its own tissue

Axon

The long, thread-like part of a *neuron*, or nerve cell, along which nerve signals are conducted

Central nervous system (CNS)

A term used to describe the brain and the spinal cord; the part of the body affected by *MS*

Cerebrospinal fluid

A clear fluid that circulates in the space surrounding the brain and spinal cord

Clinically isolated syndrome (CIS)

A first neurologic episode that lasts at least 24 hours and is caused by *inflammation/demyelination* in 1 or more sites in the *CNS*

Cognitive abilities

Cognitive abilities include memory, concentration, problem solving, and thinking

Evoked potentials

A testing method that measures electrical activity in the *CNS*

Immune system

One of the most complex biological systems, made up of an advanced network of cells, tissues, and organs that work together to provide the body with a natural system of defenses

Inflammation

The body's response to physical insult or injury, resulting in increased blood flow with swelling, tenderness, redness, and/or heat

Lesion

In *MS*, a damaged area in the brain or spinal cord caused by demyelination (also called plaque or *sclerosis*)

Magnetic resonance imaging (MRI)

A diagnostic procedure employing a special scanner to obtain detailed images of a specific area of the body, such as the brain or spinal cord

Multiple sclerosis (MS)

A disease that attacks the *CNS*. With *MS*, the *immune system* creates swelling and causes damage to the nerve coating (called *myelin*) that protects the nerve fibers in the brain and spinal cord. This damage prevents nerve cells from communicating properly to relay signals to and from other parts of the body

Myelin

A soft, white coating that surrounds and protects nerve fibers in the central and peripheral nervous systems. Myelin also helps nerve fibers conduct electrical impulses

Neurologist

A medical doctor (or physician) who specializes in conditions that affect the nervous system, such as *MS*, epilepsy, or Parkinson's disease

Neuron

The basic nerve cell of the *CNS*

Primary-progressive *MS* (PPMS)

A less common form of *MS* than the *relapsing-remitting* form. PPMS makes up approximately 10% of all cases of *MS* and is characterized by a slow but nearly continuous worsening of disease

Progressive-relapsing *MS* (PRMS)

The rarest form of *MS*, which affects approximately 5% of all newly diagnosed patients. PRMS is characterized by a steady worsening of disease after diagnosis. People with PRMS may experience clear, serious *relapses* with or without complete recovery

Relapse

A worsening of *MS* symptoms or an appearance of new symptoms (also called attack, exacerbation, or flare-up)

Relapsing-remitting MS (RRMS)

The most common form of *MS*, affecting approximately 85% of all newly diagnosed people. RRMS is characterized by *relapses* that are usually followed by partial or complete recovery

Relapsing MS

The FDA considers relapsing forms of *MS* to be inclusive of RRMS and CIS

Sclerosis


Hardening of tissue. In *MS*, sclerosis is the body's replacement of lost *myelin* around CNS cells with scar tissue (also called *lesion* or plaque). The plural of this word is *scleroses*

Secondary-progressive MS (SPMS)

A stage of *MS* that may come after RRMS. People with SPMS may have occasional *relapses*, minor remissions, and/or plateaus. Late in the course of the disease, they may experience progressive disability

T cell

One type of protective white blood cell that travels throughout the bloodstream looking for viruses, bacteria, and tumor cells. T cells play an important role in protecting the body

A woman with long brown hair and glasses, wearing a blue button-down shirt over a yellow top, is smiling and looking down at a spiral-bound notebook she is holding. A pen is resting on the notebook. The background is a bright, out-of-focus office or home workspace with shelves. A decorative blue and yellow curved banner is at the bottom of the image.

Tricia C., diagnosed with
a relapsing form of MS

MS resources

- **Multiple Sclerosis Association of America (MSAA)**
1-800-LEARN-MS (1-800-532-7667)
www.mymsaa.org
- **Multiple Sclerosis Foundation (MSF)**
1-888-MSFOCUS (1-888-673-6287)
www.msfocus.org
- **National Multiple Sclerosis Society (NMSS)**
1-800-FIGHT-MS (1-800-344-4867)
www.nationalmssociety.org
- **Can Do Multiple Sclerosis™**
1-800-367-3101
www.mscando.org
- **Caregiver Action Network**
1-202-772-5050
www.caregiveraction.org
- **Americans With Disabilities Act**
1-800-514-0301
www.ada.gov
- **Centers for Medicare & Medicaid Services**
1-877-267-2323
www.cms.gov
- **MSWorld®**
www.msworld.org
- **Shared Solutions®**
1-800-887-8100
www.sharedsolutions.com

Important Safety Information

Do not take COPAXONE® (glatiramer acetate injection) if you are allergic to glatiramer acetate or mannitol.

Some patients report a short-term reaction right after injecting COPAXONE®. This reaction can involve flushing (feeling of warmth and/or redness), chest tightness or pain with heart palpitations, anxiety, and trouble breathing. These symptoms generally appear within minutes of an injection, last about 15 minutes, and do not require specific treatment. During the postmarketing period, there have been reports of patients with similar symptoms who received emergency medical care.

If symptoms become severe, call the emergency phone number in your area. Call your doctor right away if you develop hives, skin rash with irritation, dizziness, sweating, chest pain, trouble breathing, or severe pain at the injection site. If any of the above occurs, do not give yourself any more injections until your doctor tells you to begin again.

Chest pain may occur either as part of the immediate postinjection reaction or on its own. This pain should only last a few minutes. You may experience more than one such episode, usually beginning at least one month after starting treatment. Tell your doctor if you experience chest pain that lasts for a long time or feels very intense.

A permanent indentation under the skin (lipoatrophy or, rarely, necrosis) at the injection site may occur, due to local destruction of fat tissue. Be sure to follow proper injection technique and inform your doctor of any skin changes.

The most common side effects in studies of COPAXONE® (glatiramer acetate injection) are redness, pain, swelling, itching, or a lump at the site of injection, flushing, rash, shortness of breath, and chest pain. These are not all of the possible side effects of COPAXONE®. For a complete list, ask your doctor or pharmacist. Tell your doctor about any side effects you have while taking COPAXONE®.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information on the following pages.

Important Safety
Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COPAXONE® safely and effectively. See full prescribing information for COPAXONE.

COPAXONE (glatiramer acetate injection) for subcutaneous use

Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Dosage and Administration, Recommend Dose (2.1)	01/2014
Dosage and Administration, Instructions for Use (2.2)	01/2014
Warnings and Precautions, Immediate Post-Injection Reaction (5.1)	01/2014
Warnings and Precautions, Chest Pain (5.2)	01/2014
Warnings and Precautions, Lipodystrophy and Skin Necrosis (5.3)	01/2014

INDICATIONS AND USAGE

COPAXONE is indicated for the treatment of patients with relapsing-forms of multiple sclerosis (1).

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only; doses are not interchangeable (2.1)
- COPAXONE 20 mg/mL per day (2.1)
- COPAXONE 40 mg/mL three times per week (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg/mL in a single-dose prefilled syringe with a white plunger (3)
- Injection: 40 mg/mL in a single-dose, prefilled syringe with a blue plunger (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose
- 2.2 Instructions for Use

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Immediate Post-Injection Reaction
- 5.2 Chest Pain
- 5.3 Lipodystrophy and Skin Necrosis
- 5.4 Potential Effects on Immune Response

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery

CONTRAINDICATIONS

Known hypersensitivity to glatiramer acetate or mannitol (4)

WARNINGS AND PRECAUTIONS

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipodystrophy and skin necrosis may occur. Instruct patients in proper injection technique and to rotate injection sites (5.3)
- COPAXONE can modify immune response (5.4)

ADVERSE REACTIONS

- In controlled studies of COPAXONE 20 mg/mL, most common adverse reactions ($\geq 10\%$ and ≥ 1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)
- In a controlled study of COPAXONE 40 mg/mL, most common adverse reactions ($\geq 10\%$ and ≥ 1.5 times higher than placebo) were: injection site reactions (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA at 1-800-221-4026 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known if COPAXONE is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2014

- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Use in Patients with Impaired Renal Function

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12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION**COPAXONE (glatiramer acetate injection)****1 INDICATIONS AND USAGE**

COPAXONE is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dose**

COPAXONE is for subcutaneous use only. Do not administer intravenously. The dosing schedule depends on the product strength that is selected. The recommended doses are:

- COPAXONE 20 mg per mL: administer once per day or
- COPAXONE 40 mg per mL: administer three times per week and at least 48 hours apart

COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable.

2.2 Instructions for Use

Remove one blister-packaged prefilled syringe from the refrigerated carton. Let the prefilled syringe stand at room temperature for 20 minutes to allow the solution to warm to room temperature. Visually inspect the syringe for particulate matter and discoloration prior to administration. The solution in the syringe should appear clear, colorless to slightly yellow. If particulate matter or discoloration is observed, discard the syringe.

Areas for subcutaneous self-injection include arms, abdomen, hips, and thighs. The prefilled syringe is for single use only. Discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg per mL in a single-dose, prefilled syringe with a white plunger. For subcutaneous use only.
- Injection: 40 mg per mL in a single-dose, prefilled syringe with a blue plunger. For subcutaneous use only.

4 CONTRAINDICATIONS

COPAXONE is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

5 WARNINGS AND PRECAUTIONS**5.1 Immediate Post-Injection Reaction**

Approximately 16% of patients exposed to COPAXONE 20 mg per mL in the 5 placebo-controlled trials compared to 4% of those on placebo, and approximately 2% of patients exposed to COPAXONE 40 mg per mL in a placebo-controlled trial compared to none on placebo, experienced a constellation of symptoms immediately after injection that included at least two of the following: flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. In general, these symptoms have their onset several months after the initiation of treatment, although they may occur earlier, and a given patient may experience one or several episodes of these symptoms. Whether or not any of these symptoms actually represent a specific syndrome is uncertain. Typically, the symptoms were transient and self-limited and did not require treatment; however, there have been reports of patients with similar symptoms who received emergency medical care. Whether an immunologic or nonimmunologic mechanism mediates these episodes, or whether several similar episodes seen in a given patient have identical mechanisms, is unknown.

5.2 Chest Pain

Approximately 13% of COPAXONE 20 mg per mL patients in the 5 placebo-controlled studies compared to 6% of placebo patients, and approximately 2% of patients exposed to COPAXONE 40 mg per mL in a placebo-controlled trial compared to 1% of placebo patients, experienced at least one episode of transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal

relationship of this chest pain to an injection was not always known. The pain was usually transient, often unassociated with other symptoms, and appeared to have no clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown.

5.3 Lipatrophy and Skin Necrosis

At injection sites, localized lipatrophy and, rarely, injection site skin necrosis may occur. Lipatrophy occurred in approximately 2% of patients exposed to COPAXONE 20 mg per mL in the 5 placebo-controlled trials compared to none on placebo, and 0.5% of patients exposed to COPAXONE 40 mg per mL in a single placebo-controlled trial and none on placebo. Skin necrosis has only been observed in the post-marketing setting. Lipatrophy may occur at various times after treatment onset (sometimes after several months) and is thought to be permanent. There is no known therapy for lipatrophy. To assist in possibly minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites with each injection.

5.4 Potential Effects on Immune Response

Because COPAXONE can modify immune response, it may interfere with immune functions. For example, treatment with COPAXONE may interfere with the recognition of foreign antigens in a way that would undermine the body's tumor surveillance and its defenses against infection. There is no evidence that COPAXONE does this, but there has not been a systematic evaluation of this risk. Because COPAXONE is an antigenic material, it is possible that its use may lead to the induction of host responses that are untoward, but systematic surveillance for these effects has not been undertaken. Although COPAXONE is intended to minimize the autoimmune response to myelin, there is the possibility that continued alteration of cellular immunity due to chronic treatment with COPAXONE may result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in most patients receiving glatiramer acetate. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled trial of 125 RMS patients given COPAXONE 20 mg per mL, subcutaneously every day for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested; nevertheless, anaphylaxis can be associated with the administration of most any foreign substance, and therefore, this risk cannot be excluded.

6 ADVERSE REACTIONS**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Incidence in Controlled Clinical Trials***COPAXONE 20 mg per mL per day***

Among 563 patients treated with COPAXONE in blinded placebo-controlled trials, approximately 5% of the subjects discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: injection site reactions, dyspnea, urticaria, vasodilatation, and hypersensitivity. The most common adverse reactions were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

COPAXONE® (glatiramer acetate injection)

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 20 mg per mL in the placebo-controlled trials. These signs and symptoms were numerically more common in patients treated with COPAXONE than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 1: Adverse reactions in controlled clinical trials with an incidence $\geq 2\%$ of patients and more frequent with COPAXONE (20 mg per mL daily) than with placebo

		COPAXONE 20 mg/mL (n=563)	Placebo (n=564)
Blood And Lymphatic System Disorders	Lymphadenopathy	7%	3%
Cardiac Disorders	Palpitations	9%	4%
	Tachycardia	5%	2%
Eye Disorders	Eye Disorder	3%	1%
	Diplopia	3%	2%
Gastrointestinal Disorders	Nausea	15%	11%
	Vomiting	7%	4%
	Dysphagia	2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema	43%	10%
	Injection Site Pain	40%	20%
	Injection Site Pruritus	27%	4%
	Injection Site Mass	26%	6%
	Asthenia	22%	21%
	Pain	20%	17%
	Injection Site Edema	19%	4%
	Chest Pain	13%	6%
	Injection Site Inflammation	9%	1%
	Edema	8%	2%
	Injection Site Reaction	8%	1%
	Pyrexia	6%	5%
	Injection Site Hypersensitivity	4%	0%
	Local Reaction	3%	1%
	Chills	3%	1%
	Face Edema	3%	1%
	Edema Peripheral	3%	2%
	Injection Site Fibrosis	2%	1%
	Injection Site Atrophy*	2%	0%

COPAXONE® (glatiramer acetate injection)

		COPAXONE 20 mg/mL (n=563)	Placebo (n=564)
Immune System Disorders	Hyper-sensitivity	3%	2%
Infections And Infestations	Infection	30%	28%
	Influenza	14%	13%
	Rhinitis	7%	5%
	Bronchitis	6%	5%
	Gastroenteritis	6%	4%
	Vaginal Candidiasis	4%	2%
Metabolism And Nutrition Disorders	Weight Increased	3%	1%
Musculoskeletal And Connective Tissue Disorders	Back Pain	12%	10%
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Benign Neoplasm of Skin	2%	1%
Nervous System Disorders	Tremor	4%	2%
	Migraine	4%	2%
	Syncope	3%	2%
	Speech Disorder	2%	1%
Psychiatric Disorders	Anxiety	13%	10%
	Nervousness	2%	1%
Renal And Urinary Disorders	Micturition Urgency	5%	4%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	14%	4%
	Cough	6%	5%
	Laryngospasm	2%	1%
Skin And Subcutaneous Tissue Disorders	Rash	19%	11%
	Hyperhidrosis	7%	5%
	Pruritus	5%	4%
	Urticaria	3%	1%
	Skin Disorder	3%	1%
Vascular Disorders	Vasodilatation	20%	5%

*Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4 to 5 more subjects in the COPAXONE group than in the placebo group (less than 1% difference), but for which a relationship to COPAXONE could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE. Clinically-significant laboratory values for hematology, chemistry, and

urinalysis were similar for both COPAXONE and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia ($16 \times 10^9/L$), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials of COPAXONE 20 mg per mL were analyzed to evaluate differences based on sex. No clinically-significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with COPAXONE were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age subgroups.

Other Adverse Reactions

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies ($n=979$), the role of COPAXONE in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used COPAXONE and reported a reaction divided by the total number of patients exposed to COPAXONE. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

Body as a Whole:

Frequent: Abscess.

Infrequent: Injection site hematoma, moon face, cellulitis, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.

Cardiovascular:

Frequent: Hypertension.

Infrequent: Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency, and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

COPAXONE 40 mg per mL three times per week

Among 943 patients treated with COPAXONE 40 mg per mL three times per week in a blinded, placebo-controlled trial, approximately 3% of the subjects discontinued treatment because of an adverse reaction. The most common adverse reactions were injection site reactions, which were also the most common cause of discontinuation.

Table 2 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients treated with COPAXONE 40 mg per mL in the blinded, placebo-controlled trial. These signs and symptoms were numerically more common in patients treated with COPAXONE 40 mg per mL than in patients treated with placebo. Adverse reactions were usually mild in intensity.

Table 2: Adverse reactions in a controlled clinical trial with an incidence $\geq 2\%$ of patients and more frequent with COPAXONE (40 mg per mL three times per week) than with placebo

		COPAXONE 40 mg/mL (n=943)	Placebo (n=461)
General Disorders And Administration Site Conditions	Injection Site Erythema	22%	2%
	Injection Site Pain	10%	2%
	Injection Site Mass	6%	0%
	Injection Site Pruritus	6%	0%

COPAXONE® (glatiramer acetate injection)

		COPAXONE 40 mg/mL (n=943)	Placebo (n=461)
	Injection Site Edema	6%	0%
	Pyrexia	3%	2%
	Influenza-like Illness	3%	2%
	Injection Site Inflammation	2%	0%
	Chills	2%	0%
	Chest Pain	2%	1%
Infections And Infestations	Nasopharyngitis	11%	9%
	Respiratory Tract Infection Viral	3%	2%
Respiratory, Thoracic And Mediastinal Disorders	Dyspnea	3%	0%
Vascular Disorders	Vasodilatation	3%	0%
Gastrointestinal Disorders	Nausea	2%	1%
Skin And Subcutaneous Tissue Disorders	Erythema	2%	0%
	Rash	2%	1%

No new adverse reactions appeared in subjects treated with COPAXONE 40 mg per mL three times per week as compared to subjects treated with COPAXONE 20 mg per mL per day in clinical trials and during postmarketing experience. Data on adverse reactions occurring in the controlled clinical trial of COPAXONE 40 mg per mL were analyzed to evaluate differences based on sex. No clinically significant differences were identified. Ninety-eight percent of patients in this clinical trial were Caucasian and the majority were between the ages of 18 and 50. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age groups.

6.2 Postmarketing Experience

The following adverse events occurring under treatment with COPAXONE 20 mg per mL since market introduction and not mentioned above have been identified during postapproval use of COPAXONE. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction; anaphylactoid reaction
Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris
Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia
Musculoskeletal System: rheumatoid arthritis; generalized spasm

COPAXONE® (glatiramer acetate injection)

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasia; convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung

Special Senses: glaucoma; blindness

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

7 DRUG INTERACTIONS

Interactions between COPAXONE and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. COPAXONE has not been formally evaluated in combination with interferon beta.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category B.

Administration of glatiramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, COPAXONE should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatiramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/m² basis). In rats receiving subcutaneous glatiramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

8.2 Labor and Delivery

The effects of COPAXONE on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known if glatiramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COPAXONE is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of COPAXONE have not been established in patients under 18 years of age.

8.5 Geriatric Use

COPAXONE has not been studied in elderly patients.

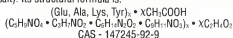
8.6 Use in Patients with Impaired Renal Function

The pharmacokinetics of glatiramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION

Glatiramer acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 daltons. Glatiramer acetate is identified by specific antibodies.

Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



COPAXONE is a clear, colorless to slightly yellow, sterile, non-pyrogenic solution for subcutaneous injection. Each 1 mL of COPAXONE solution contains 20 mg or 40 mg of glatiramer acetate and the following inactive ingredient: 40 mg of mannitol. The pH of the solutions is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS are not fully understood. However, glatiramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatiramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatiramer acetate can modify immune functions, concerns exist about its potential to alter naturally-occurring immune responses. There is no evidence that glatiramer acetate does this, but this has not been systematically evaluated [see Warnings and Precautions (5.4)].

12.3 Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m² basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatiramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in neoplasms was observed.

Glatiramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatiramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatiramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m² basis) no adverse effects were observed on reproductive or developmental parameters.

14 CLINICAL STUDIES

Evidence supporting the effectiveness of COPAXONE derives from five placebo-controlled trials, four of which used a COPAXONE dose of 20 mg per mL per day and one of which used a COPAXONE dose of 40 mg per mL three times per week.

COPAXONE 20 mg per mL per day

Study 1 was performed at a single center. Fifty patients were enrolled and randomized to receive daily doses of either COPAXONE, 20 mg per mL subcutaneously, or placebo (COPAXONE: n=25; placebo: n=25). Patients were diagnosed with RMS by standard criteria, and had had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients were ambulatory, as evidenced by a score of no more than 6 on the Kurtzke Disability Scale Score (DSS), a standard scale ranging from 0-Normal to 10-Death due to MS. A score of 6 is defined as one at which a patient is still ambulatory with assistance; a score of 7 means the patient must use a wheelchair.

Patients were examined every 3 months for 2 years, as well as within several days of a presumed exacerbation. To confirm an exacerbation, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the neurological signs for at least 48 hours).

The protocol-specified primary outcome measure was the proportion of patients in each treatment group who remained exacerbation free for the 2 years of the trial, but two other important outcomes were also specified as endpoints: the frequency of attacks during the trial, and the change in the number of attacks compared with the number which occurred during the previous 2 years.

Table 3 presents the values of the three outcomes described above, as well as several protocol-specified secondary measures. These values are based on the intent-to-treat population (i.e., all patients who received at least 1 dose of treatment and who had at least 1 on-treatment assessment):

Table 3: Study 1 Efficacy Results

	COPAXONE 20 mg/mL (n=25)	Placebo (n=25)	P-Value
% Relapse-Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate Compared to Prestudy	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

*Progression was defined as an increase of at least 1 point on the DSS, persisting for at least 3 consecutive months.

Study 2 was a multicenter trial of similar design which was performed in 11 US centers. A total of 251 patients (COPAXONE: n=125; placebo: n=126) were enrolled. The primary outcome measure was the Mean 2-Year Relapse Rate. Table 4 presents the values of this outcome for the intent-to-treat population, as well as several secondary measures:

COPAXONE® (glatiramer acetate injection)

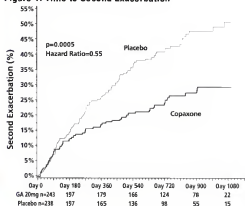
Table 4: Study 2 Efficacy Results

	COPAXONE 20 mg/mL (n=125)	Placebo (n=126)	P-Value
Mean No. of Relapses	1.19/2 years	1.68/2 years	0.055
% Relapse-Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Progression-Free Patients	98/125 (78%)	95/126 (75%)	0.48
Mean Change in DSS	-0.05	+0.21	0.023

In both studies, COPAXONE exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that COPAXONE is considered effective.

In Study 3, 481 patients who had recently (within 90 days) experienced an isolated demyelinating event and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either COPAXONE 20 mg per mL (n=243) or placebo (n=238). The primary outcome measure was time to development of a second exacerbation. Patients were followed for up to three years or until they reached the primary endpoint. Secondary outcomes were brain MRI measures, including number of new T2 lesions and T2 lesion volume. Time to development of a second exacerbation was significantly delayed in patients treated with COPAXONE compared to placebo (Hazard Ratio = 0.55; 95% confidence interval 0.40 to 0.77; Figure 1). The Kaplan-Meier estimates of the percentage of patients developing a relapse within 36 months were 42.9% in the placebo group and 24.7% in the COPAXONE group.

Figure 1: Time to Second Exacerbation



Patients treated with COPAXONE demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with COPAXONE (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RRMS (COPAXONE: n=119; and placebo: n=120) were randomized. Inclusion criteria were

COPAXONE® (glatiramer acetate injection)

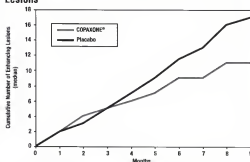
similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 5 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 5: Study 4 MRI Results

	COPAXONE 20 mg/mL (n=119)	Placebo (n=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

Figure 2 displays the results of the primary outcome on a monthly basis.

Figure 2: Median Cumulative Number of Gd-Enhancing Lesions



COPAXONE 40 mg per mL three times per week

Study 5 was a double-blind, placebo-controlled, multinational study with a total of 1404 patients with RRMS randomized in a 2:1 ratio to receive either COPAXONE 40 mg per mL (n=943) or placebo (n=461) three times a week for 12 months. Patients had a median of 2 relapses in the 2 years prior to screening and had not received any interferon-beta for at least 2 months prior to screening. Baseline EDSS scores ranged from 0 to 5.5 with a median of 2.5. Neurological evaluations were performed at baseline, every three months, and at unscheduled visits for suspected relapse or early termination. MRI was performed at baseline, months 6 and 12, or early termination. A total of 91% of those assigned to COPAXONE and 93% of those assigned to placebo completed treatment at 12 months.

The primary outcome measure was the total number of confirmed relapses (persistence of neurological symptoms for at least 24 hours confirmed on examination with objective signs). The effect of COPAXONE on several magnetic resonance imaging (MRI) variables, including number of new or enlarging T2 lesions and number of enhancing lesions on T1-weighted images, was also measured at months 6 and 12.

Table 6 presents the results for the intent-to-treat population.

COPAXONE® (glatiramer acetate injection)**Table 6: Study 5 Efficacy and MRI Results**

	COPAXONE 40 mg/mL (n=943)	Placebo (n=461)	P-Value
Clinical Endpoints			
Number of confirmed relapses during the 12-month placebo-controlled phase			
Adjusted Mean Estimates	0.331	0.505	<0.0001
Relative risk reduction	34%		
MRI Endpoints			
Cumulative number of new or enlarging T2 lesions at Months 6 and 12			
Adjusted Mean Estimates	3.650	5.592	<0.0001
Relative risk reduction	35%		
Cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12			
Adjusted Mean Estimates	0.905	1.639	<0.0001
Relative risk reduction	45%		

16 HOW SUPPLIED/STORAGE AND HANDLING

COPAXONE (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister packages supplied in 30-count cartons (NOC 68546-317-30).
- 40 mg per mL in a single-dose, prefilled syringe with a blue plunger, in individual blister packages supplied in 12-count cartons (NOC 68546-325-12).

Store COPAXONE refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store COPAXONE at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze COPAXONE. If a COPAXONE syringe freezes, it should be discarded.

17 PATIENT COUNSELING INFORMATION

[See Patient Information Leaflet (Patient Information and Instructions for Use)]

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking COPAXONE they should inform their physician.

Immediate Post-Injection Reaction

Advise patients that COPAXONE may cause various symptoms after injection, including flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

Chest Pain

Advise patients that they may experience transient chest pain either as part of the Immediate Post-Injection Reaction or in isolation. Inform patients that the pain should be transient. Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patients should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

COPAXONE® (glatiramer acetate injection)**Lipoatrophy and Skin Necrosis at Injection Site**

Advise patients that localized lipoatrophy, and rarely, skin necrosis may occur at injection sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Instructions for Use

Instruct patients to read the COPAXONE Patient Information leaflet carefully. COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable. COPAXONE 20 mg per mL is administered daily and COPAXONE 40 mg per mL is administered three times per week. Caution patients to use aseptic technique. The first injection should be performed under the supervision of a health care professional. Instruct patients to rotate injection areas and sites with each injection. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

Storage Conditions

Advise patients that the recommended storage condition for COPAXONE is refrigeration at 36°F to 46°F (2°C to 8°C). If needed, the patient may store COPAXONE at room temperature, 59°F to 86°F (15°C to 30°C), for up to one month, but refrigeration is preferred. COPAXONE should not be exposed to higher temperatures or intense light. Do not freeze COPAXONE.

TEVA Neuroscience

Marketed by: TEVA Neuroscience, Inc., Overland Park, KS 66211
Distributed by: TEVA Pharmaceuticals USA, Inc., North Wales, PA 19454
Product of Israel

Patient Information
COPAXONE (co-PAX-own)
(glatiramer acetate injection)
for subcutaneous use

Read this Patient Information before you start using COPAXONE and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is COPAXONE?

COPAXONE is prescription medicine used for the treatment of people with relapsing forms of multiple sclerosis (MS).

It is not known if COPAXONE is safe and effective in children under 18 years of age.

Who should not use COPAXONE?

- Do not use COPAXONE if you are allergic to glatiramer acetate, mannitol or any of the ingredients in COPAXONE. See the end of this leaflet for a complete list of the ingredients in COPAXONE.

What should I tell my doctor before using COPAXONE?**Before you use COPAXONE, tell your doctor if you:**

- are pregnant or plan to become pregnant. It is not known if COPAXONE will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if COPAXONE passes into your breast milk. Talk to your doctor about the best way to feed your baby while using COPAXONE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. COPAXONE may affect the way other medicines work, and other medicines may affect how COPAXONE works.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I use COPAXONE?

- For detailed instructions, see the **Instructions for Use** at the end of this leaflet for complete information on how to use COPAXONE.
- Your doctor will tell you how much COPAXONE to use and when to use it.
- COPAXONE is given by injection under your skin (subcutaneously).
- Use COPAXONE exactly as your doctor tells you to use it.
- Since every body type is different, talk with your doctor about the injection areas that are best for you.
- You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will teach you how to give your COPAXONE injections.

What are the possible side effects of COPAXONE? COPAXONE may cause serious side effects, including:

- **Post-Injection Reactions.** Serious side effects may happen right after you inject COPAXONE at any time during your course of treatment. Call your doctor right away if you have any of these post-injection reaction symptoms including:
 - redness to your cheeks or other parts of the body (flushing)
 - chest pain
 - fast heart beat
 - anxiety
 - breathing problems or tightness in your throat
 - swelling, rash, hives, or itching

If you have symptoms of a post-injection reaction, do not give yourself more injections until a doctor tells you to.

- **Chest Pain.** You can have chest pain as part of a post-injection reaction or by itself. This type of chest pain usually lasts a few minutes and can begin around 1 month after you start using COPAXONE. Call your doctor right away if you have chest pain while using COPAXONE.
- **Damage to your skin.** Damage to the fatty tissue just under your skin's surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use COPAXONE. Damage to the fatty tissue under your skin can cause a "dent" at the injection site that may not go away. You can reduce your chance of developing these problems by:
 - following your doctor's instructions for how to use COPAXONE
 - choosing a different injection area each time you use COPAXONE. **See Step 4 in the Instructions for Use, "Choose your injection area".**

The most common side effects of COPAXONE include:

- skin problems at your injection site including:
 - redness
 - pain
 - swelling
 - itching
 - lumps
- rash
- shortness of breath
- flushing (vasodilation)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of COPAXONE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COPAXONE?

- Store COPAXONE in the refrigerator between 36°F to 46°F (2°C to 8°C).
- When you are not able to refrigerate COPAXONE, you may store it for up to 1 month at room temperature between 59°F to 86°F (15°C to 30°C).
- Protect COPAXONE from light or high temperature.
- Do not freeze COPAXONE syringes. If a syringe freezes, throw it away in a sharps disposal container. **See Step 13 in the Instructions for Use, "Dispose of needles and syringes".**

Keep COPAXONE and all medicines out of the reach of children.

General information about the safe and effective use of COPAXONE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use COPAXONE for a condition for which it was not prescribed. Do not give COPAXONE to other people, even if they have the same symptoms as you have. It may harm them. This Patient Information Leaflet summarizes the most important information about COPAXONE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about COPAXONE that is written for health professionals.

For more information, go to www.copaxone.com or call 1-800-887-8100.

What are the ingredients in COPAXONE?

Active ingredient: glatiramer acetate

Inactive ingredients: mannitol

Instructions for Use

**COPAXONE (co-PAX-own)
(glatiramer acetate injection)
for subcutaneous use**

For subcutaneous injection only.

Do not inject COPAXONE in your veins (intravenously).

Do not re-use your COPAXONE prefilled syringes.

Do not share your COPAXONE prefilled syringes with another person. You may give another person an infection or get an infection from them.

You should receive your first dose of COPAXONE with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will show you how to give your own injections.

COPAXONE comes in either a 20 mg Prefilled Syringe with needle attached or a 40 mg Prefilled Syringe with needle attached. How often a dose is given depends on the product strength that is prescribed. Your doctor will prescribe the correct dose for you.

Instructions for Using Your COPAXONE 20 mg Prefilled Syringe dose:

- **COPAXONE 20 mg** is injected 1 time each day, in the fatty layer under your skin (subcutaneously).
- Each COPAXONE 20 mg prefilled syringe is for single use (1 time use) only.
- The COPAXONE 20 mg dose is packaged in boxes of 30 prefilled syringes with needles attached. COPAXONE 20 mg prefilled syringes have **white** plungers.

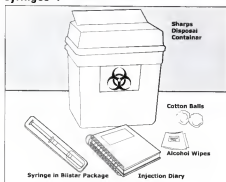
Instructions for Using Your COPAXONE 40 mg Prefilled Syringe:

- **COPAXONE 40 mg** is injected 3 times each week in the fatty layer under your skin (subcutaneously).
- COPAXONE 40 mg should be given on the same 3 days each week, if possible for example, Monday, Wednesday, and Friday. Give your COPAXONE injections at least 48 hours (2 days) apart.
- Each COPAXONE 40 mg prefilled syringe is for single use (1 time use) only.
- The COPAXONE 40 mg dose is packaged in boxes of 12 prefilled syringes with needles attached. COPAXONE 40 mg prefilled syringes have **blue** plungers.

How do I inject COPAXONE?

Step 1: Gather the supplies you will need to inject COPAXONE. **See Figure A.**

- 1 blister pack with a COPAXONE Prefilled Syringe with needle attached
- Alcohol wipe (not supplied)
- Dry cotton ball (not supplied)
- A place to record your injections, like a notebook (not supplied)
- Sharps disposal container (not supplied). **See Step 13 below, "Dispose of needles and syringes".**

**Figure A**

Step 2: Remove only 1 blister pack from the COPAXONE prefilled syringe carton. **See Figure B.**

**Figure B**

- Place the supplies you will need on a clean, flat surface in a well-lit area.

COPAXONE® (glatiramer acetate injection)

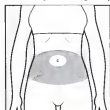
- After you remove 1 blister pack from the carton, keep all unused syringes in the carton and store them in the refrigerator.
- Let the blister pack, with the syringe inside, warm to room temperature for about 20 minutes.
- Wash your hands. Be careful not to touch your face or hair after washing your hands.

Step 3: Look closely at your COPAXONE prefilled syringe.

- There may be small air bubbles in the syringe. **Do not** try to push the air bubble from the syringe before giving your injection so you do not lose any medicine.
- Check the liquid medicine in the syringe before you give your injection. The liquid in the syringe should look clear, and colorless, and may look slightly yellow. If the liquid is cloudy or contains any particles, do not use the syringe and throw it away in a sharps disposal container. **See Step 13 below, "Dispose of needles and syringes."**

Step 4: Choose your injection area. See Figure C. See the injection areas you should use on your body. Talk with your doctor about the injection areas that are best for you.

- The possible injection areas on your body include (**See Figure C**):
 - your stomach area (abdomen) around the belly button
 - the back of your upper arms
 - upper hips (below your waist)
 - your thighs (above your knees)

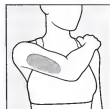


Abdomen
Avoid about 2 inches around the belly button



Back of Hips and Arms
Fleshy areas of the upper hips, always below the waist

Fleshy areas of the upper back portion of the arms



Arms
Fleshy areas of the upper back portion



Thighs
About 2 inches above the knee and 2 inches below the groin

Figure C

COPAXONE® (glatiramer acetate injection)

- For each COPAXONE dose, choose a different injection area from 1 of the areas shown above. **See Figure C.**
- **Do not stick the needle in the same place (site) more than 1 time each week.** Each injection area contains multiple injection sites for you to choose from. Avoid injecting in the same site over and over again.
- Keep a record of the sites where you give your injection each day so you will remember where you already injected.

Step 5: Prepare to give your injection.

- There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.
- Do not inject in sites where the skin has scarring or "dents". Using scarred or dented skin for your injections may make your skin worse.

Step 6: Clean your injection site.

- Clean the injection site using the alcohol wipe and allow your skin to air dry. **See Figure D.**



Figure D

Step 7: Pick up the syringe with 1 hand and hold it like a pencil. Remove the needle cover with your other hand and set it aside. See Figure E.



Figure E

Step 8: Pinch about a 2 inch fold of skin between your thumb and index finger. See Figure F.



Figure F

Step 9: Giving your injection.

- Rest the heel of your hand holding the syringe against your skin at the injection site. Insert the needle at a 90 degree angle straight into your skin. **See Figure G.**

**Figure G**

- When the needle is all the way into your skin, release the fold of skin. **See Figure H.**

**Figure H**

Step 10: Give your COPAXONE injection.

To inject the medicine, hold the syringe steady and slowly push down the plunger. **See Figure I.**

**Figure I**

Step 11: Remove the needle.

After you have injected all of the medicine, pull the needle straight out. **See Figure J.**

**Figure J**

Step 12: Use a clean, dry cotton ball to gently press on the injection site for a few seconds. Do not rub the injection site or re-use the needle or syringe. **See Figure K.**

**Figure K**

Step 13: Dispose of your needles and syringes.

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

**Figure L**

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.



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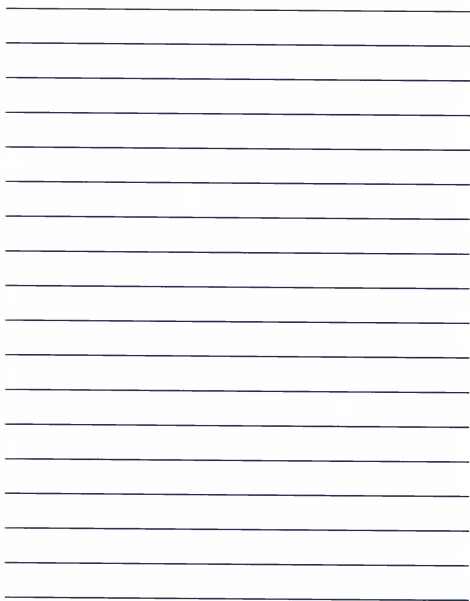
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Tricia C., diagnosed with
a relapsing form of MS



**Please see Important Safety Information on pages 26 and 27,
and full Prescribing Information on pages 28-39.**

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